REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Office Action dated February 10, 2005. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 1-9 are pending in this application. Claim 1 is being amended to more particularly point out and distinctly claim the subject invention. Applicant hereby submits that no new matter is being introduced into the application through the submission of this response.

Prior Art Rejections

Claims 1-6 and 8 were rejected under 35 U.S.C. § 102(b) as being anticipated by Eisen et al. published on PNAS, vol. 95, pp. 14863-14868, Dec. 1998 (hereinafter "Eisen"), and against claim 7 under 35 U.S.C. § 103(a) as being unpatentable over Eisen in view of an article by Lockhart published on Nature Biotechnology. Vol. 14, pp. 11675-1680 1996 (hereinafter "Lockhart"). Claims 1 and 9 were rejected under 35 U.S.C. § 102(e) as being anticipated by U.S. Pat. No. 6,344,316 Lockhart et al. (Lockhart' 316), and against claims 2-8 under 35 U.S.C. § 103(a) as being unpatentable over Lockhart et al. in view of an article on FEMS Microbiology Letters, 175, pp.247-250, 1999 by Tatusova et al (hereinafter "Tatusova") and U.S. Patent No. 6,528,264 to Pal et al. (hereinafter "Pal"). These rejections have been carefully considered, but are most respectfully traversed.

The present invention as now claimed is directed to a method for displaying results of a hybridization experiment in which a plurality of probe biopolymers *immobilized* on a biochip" p. 6, lines 7-8) are hybridized to a sample biopolymer. The method incorporates the steps of providing the biochip immobilized with said plurality of probe biopolymers; conducting the hybridization experiment on the provided biochip thereby hybridizing said sample biopolymer with said plurality of probe biopolymers; determining information

obtained in the conducted hybridization experiment about a hybridization level for each of the probe biopolymers; determining a probe ***homologous*** similarity score(e.g., Fig. 7; p. 13, lines 19-24), which represents a homologous similarity between first probe data 301 (e.g., Fig. 5 including probe ID, name, definition, sequence, etc) on a base sequence of at least one of the probe biopolymers immobilized on the provided biochip and second probe data on a base sequence of at least one other of the probe biopolymers immobilized on the provided biochip, according to an algorithm for calculating degrees of homology between two biopolymer sequence (e.g., Smith-Waterman method, BLAST, or the like (p. 3, lines 7 and 11); "*Many other algorithms have been developed for the same purpose. In these approaches, the degrees of homology between two DNA sequences are expressed by indices such as "homology score," ... or by "matching rate,"*" p. 3, lines 7-23); and displaying (1) the information about the ***hybridization*** level (e.g., 705 in Fig. 12; 807 in Figs. 13-14) for each of the probe biopolymers together with (2) the probe homologous similarity score (808 in Figs. 13-14), including generating a visual graphical representation of the determined hybridization level and correspondingly determined probe homologous similarity score (e.g., Fig. 18) so as to provide at least one of a visual confirmation of similarities between the base sequences of corresponding probe biopolymers immobilized on the provided biochip used in the hybridization experiment and **a visual indication of unexpected or improper hybridization**.

Taking Fig. 16 as an example, a framed portion 809 in the hybridization-level data 807 indicates that the hybridization level of Probe 1 is very close to that of Probe 2 in Chip 2. A framed portion 810 in the probe homologous similarity score pattern 808 confirms that the sequences of the DNA probes, Probe 1 and Probe 2, are in fact very homology similar to one another (p. 17, last paragraph). Taking Fig. 18 as another example, the probe homologous similarity score pattern matrix 901 shows that Probe 1 and Probe 2 have very similar physical DNA sequences, but the tree diagram 1001 indicates that the probes have rather different homologous properties from one another (Probe 1 is more closely related to Probe 4). Regarding Fig. 18, although both the hybridization-level data and the probe homologous similarity score pattern matrix 901 show that Probe 1 and Probe 2 have very similar physical DNA sequences, but the tree diagram 1001 indicates that the probes have rather different homologous properties from one another (Probe 1 is more closely related to Probe 4). The hybridization-level data reflect the physical similarity of the DNA probes 1 & 2, while the

probe homologous similarity score may be partially influenced by their physical similarity, rather than only reflects their homologous similarity (p. 19, last paragraph). In other words, the sample DNA molecules of the same type bind to two different types of DNA probes 1 & 2 that are physically very similar to one another, i.e., unintended hybridization or miss-hybridization(p. 2, lines 12-17). Accordingly, the invention "*determines if unintended hybridization has occurred by observing the hybridization-level information in the proximity of the object probe. Also, by selecting the information to be displayed with the similarity score matrix, the verification of the accuracy of the hybridization is possible in wider ranges* (p. 8, lines 4-9)".

Applicants respectfully contend that neither Eisen nor Lockhart teaches or suggests at least "determining a **probe homologous similarity** score according to an algorithm for calculating degrees of homology between two biopolymer sequences" and then "displaying said information about the hybridization level for each of the probe biopolymers together with said probe homologous similarity score" so as to provide a visual indication of unexpected or improper hybridization according to the invention.

Contrary to the Examiner's assertion that Eisen's "metric (algorithm) contains similarity scores for all pair of GENEs, hence Probe biopolymer versus Probe biopolymer (p. 10, lines 8-9 of the outstanding Office Action)," Applicants respectfully contend that Eisen's similarity scores between genes are essentially different from the similarity scores between gene probes according to the invention. As defined in dictionaries, a Gene is a fundamental physical and functional unit of heredity. A gene is an ordered sequence of nucleotides located in a particular position on a particular chromosome that encodes a specific functional product (i.e., a protein or RNA molecule). See Science and Biotechnology http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=hybridization+probe. On the other hand, a gene Probe (hybridization probe) is a single-stranded nucleic acid molecule with a known nucleotide sequence which is labeled in some way (for example, radioactively, fluorescently, or immunologically) and used to find and mark certain DNA or RNA sequences of interest to a researcher by hybridizing to it. See Science and Biotechnology http://biotech.icmb.utexas.edu/search/dict-search.phtml?title=gene&search_type=beg. A gene probe can be used to locate a specific gene in a particular chromosome. A gene that has been cloned or copied becomes a labeled probe when a radioactive atom is added to it. The probe will seek out its mirror-image segment of DNA and bind to it. The radioactive probe can then

be detected by sophisticated photographic techniques. See on-line article Gene Technology available at http://www.merck.com/mmhe/sec01/ch002/ch002c.html. In particular, Eisen's genes X. Y were not immobilized on a biochip or hybridized to any sample biopolymers as gene probes of the invention.

In contrast, Eisen's yeast expression analysis (same as P. Brown's group of the Stanford University referenced on p. 4 line 3 of the specification) merely (i) calculates a gene similarity coefficient for any two genes/samples X and Y over a series of N conditions (i.e., *sample vs. sample*, or *gene vs. gene*, p. 14864, left col.) , and (ii) indicates a hybridization level between a probe ***A*** and a sample ***B*** (*probe vs. sample* p. 4, lines 2-18), but not calculates according to an algorithm for calculating degrees of homology between two probe sequences to obtain "probe homologous similarity scores" which reflect homologous similarity between any two probes (*probe vs. probe*). "*No practical approach is known for determining if a probe biopolymer has been accurately hybridized to a sample biopolymer of interest, and accordingly, there is a need for such a method* (p.4, lines 19-22)."

In addition, since Eisen's gene similarity coefficients or the metrics in Fig. 2 were obtained for genes X, Y but not for any probes, the data is used to provide a visual indication "to identify the highest value (representing the most similar pair of genes) (p. 9, lines 17-18 of the outstanding Office Action)," but not any visual indication of **unexpected or improper hybridization** as the above-discussed example shown in Fig. 18 of the specification. The invention is specifically directed to displaying the probe homologous similarity score along with and hybridization-level data are displayed side-by-side so to be compared with each other in a manner that is visually easy to understand (p. 5, lines 5-11). The probe homologous similarity score is represented by square patterns having varying color depths (rather than any cluster tree), so as to make the displayed image, and consequently the information being represented, more visually intuitive (p. 6, lines 14-19).

Lockhart' 316 merely "*lines up **a** proposed **probe** with all known **genes** for the organism being monitored, then count the number of matchingbases* (col. 39, lines 12-14)", i.e., ***probe vs. genes***, rather than calculating any "probe homologous similarity score" between the probes (***probe vs. probe***) as the present invention. Alternatively, Lockhart' 316 uses "*BLAST, or FASTA, or other gene matching programs* (col. 39, lines 34-38)" to align a probe sequence (e.g., a probe from gene 1 on col. 39) with a gene sequence (e.g., gene 2 on

col. 39) for comparing their similarity (***probe vs. genes***), rather than calculating any "probe homologous similarity score" between the probes (***probe vs. probe***) as the present invention.

In addition, Lockhart' 316 uses "*BLAST, or FASTA, or other gene matching programs* (col. 39, lines 34-38)" to align a probe sequence with a gene sequence for comparing their ***physical*** similarity (i.e., example listed in col. 39; "*comparing two optimally aligned sequences or subsequences over a comparison window or span, wherein the portion of the polynucleotide sequence in the comparison window may optionally comprise additions or deletions (i.e., gaps) as compared to the reference sequence (which does not comprise additions or deletions) for optimal alignment of the two sequences.... calculated using the programs GAP or BESTFIT etc*" col. 9, lines 50-65), rather than calculating any "probe ***homologous*** similarity score" between the probes as the present invention.

Moreover, rather than calculating any "probe homologous similarity score" between the probes ***already immobilized*** on a biochip as the present invention, Lockhart' 316's probe-gene alignment is conducted on "*a proposed probe* (col. 39, lines 12-13)" ***before*** spotting it onto a biochip or conducting the hybridization experiment thereon so as to "prune/*remove probes which are similar to more than one gene* (col. 39, line 8)" from the design of a biochip and the hybridization experiment to be conducted thereon thereby resolving the problem of "*poor signals in expression chips is that genes other than the ones being monitored have sequences which are very similar to parts of the sequences which are being monitored* (col. 39, lines 4-7)".

Contrary to the Examiner's assertion that Lockhart' 316 teaches "determining a probe homologous similarity score, which represents a homologous similarity between first probe data on a base sequence of at least one of the probe biopolymers and second probe data on a base sequence of at least one other of the probe biopolymers, according to an algorithm for calculating degrees of homology between two biopolymer sequences, wherein said algorithm is a Smith-Waterman method or a BLAST method. (p. 12, lines 1-5 of the outstanding Office Action)," Applicants respectfully contend that Lockhart' 316's **physical** similarity scores between a *proposed* probe of one gene (e.g., a probe from gene 1) and other genes (i.e., gene 2) are essentially different from the **homologous** similarity scores between two probes according to the invention. Two probes of the invention are **homologously** similar, if they are alike because of shared ancestry. Two probes of the invention are not homologously similar (e.g., probe 2 and probe 1 in Fig. 18), if they are just *physically* alike but not having shared

ancestry. On the other hand, Lockhart' 316's *proposed* probe of gene 1 is already known not homologous with gene 2 but just *physically* alike.

Further more, since the probe-gene **physical** similarity calculation of Lockhart'316 is obtained for a probe vs. genes, but not for any two probes, the data is used to "prune/*remove probes which are similar to more than one gene* (col. 39, line 8)" from the design of a biochip and the hybridization experiment to be conducted thereon, but not to provide any visual indication of **unexpected or improper hybridization** as the above-discussed example shown in Fig. 18 of the specification. The invention is specifically directed to displaying the probe homologous similarity score along with and hybridization-level data are displayed side-by-side so to be compared with each other in a manner that is visually easy to understand (p. 5, lines 5-11). The probe homologous similarity score is represented by square patterns having varying color depths (rather than any cluster tree), so as to make the displayed image, and consequently the information being represented, more visually intuitive (p. 6, lines 14-19). On the other hand, Lockhart'316 only displays, for example, a fluorescent image of a high density array containing over 16,000 different oligonucleotide probes vs. 13 specific RNA targets (Fig. 2A; col. 10, lines 33-39) which merely provides visual indication "*the amount of labeled RNA hybridized to the particular oligonucleotide probe* (col. 10, lines 40-41)."

The Examiner relied upon the "intuition of a biologist (p. 12, line 8-9 of the outstanding Office Action)" for the motivation to "display said information about the hybridization level for each of the probe biopolymers immobilized on the provided biochip together with said probe homologous similarity score, including generating a visual graphical representation of the determined hybridization level and correspondingly determined probe homologous similarity score so as to provide at least one of a visual confirmation of similarities between the base sequences of corresponding probe biopolymers immobilized on the provided biochip used in the hybridization experiment and a visual indication of unexpected or improper hybridization" in view of Lockhart'316 did not fulfill the agency's obligation to cite references, e.g., statement in the prior art, to support its conclusions. Instead, the Examiner must provide the specific teaching of such an "intuition" on the record to allow accountability.

> *To establish a prima facie case of obviousness, the Board must, inter alia, show "some objective teaching in the prior art or that knowledge generally available*

to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references." In re Fine, *837 F.2d 1071, 1074, 5 USPQ2d 1596, 1598 (Fed. Cir. 1988). "The motivation, suggestion or teaching may come explicitly from statements in the prior art, the knowledge of one of ordinary skill in the art, or, in some cases the nature of the problem to be solved."* Kotzab, *217 F.3d at 1370, 55 USPQ2d at 1317. .... Recently, in* In re Lee, *277 F.3d 1338, 61 USPQ2d 1430 (Fed. Cir. 2002), we held that the Board's reliance on "common knowledge and common sense" did not fulfill the agency's obligation to cite references to support its conclusions.* Id. *at 1344, 61 USPQ2d at 1434. Instead, the Board must document its reasoning on the record to allow accountability.* Id. *at 1345, 61 USPQ2d at 1435.*

See In re Thrift, 298 F.3d 1357.

Lockhart merely quantitatively relates hybridization intensities of mRNAs, i.e., samples, to arrays of synthetic oligonucleotides, i.e., probes (*sample vs. probe* p. 1675, left col., lines 5-8; "*RNA concentration*" Fig. 3; "*A total of 21 murine RNAs were detected at levels ranging from approximately 1:300,000 to 1:100.*" Fig. 5), rather than calculating any "probe homologous similarity score" between the probes immobilized on a biochip (*probe vs. probe*). Lockhart shares the same deficiencies as Lockhart'316.

Tatusova was relied upon by the Examiner to teach a graphic representation of sequences compared using BLAST in a dot blot picture etc. However, Tatusova (Abstract) only aligns two protein or two nucleotide sequences DNA-DNA (*sample vs. sample* or *gene vs. gene*) for comparing their **physical/local** similarity (p. 247, left col. Line 3), rather than calculating any "probe **homologous** similarity score" between any two probes (*probe vs. probe*) as the present invention.

Pal was relied upon by the Examiner to teach displaying intensity of signals with color differentiation and comparing different biochips. However, Pal fails to compensate for Lockhart's deficiencies since Pal does not disclose, teach or suggest calculating and displaying the "***probe homologous similarity*** score" along with the hybridization levels as the present invention.

Although the invention applies general homology analysis, such as Smith-Waterman method or BLAST (p. 3, lines 7 and 11), the invention applies the homology analysis

between probes immobilized on a biochip rather than between a proposed probe and a sample and then displays the *"probe homologous similarity score"* along with the hybridization levels to achieve unexpected results or properties, for example, determining if unintended hybridization occurs (Fig. 18). The presence of the unexpected properties is evidence of nonobviousness. MPEP§716.02(a).

> *"Presence of a property not possessed by the prior art is evidence of nonobviousness. In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); Ex parte Thumm, 132 USPQ 66 (Bd. App. 1961) (Appellant showed that the claimed range of ethylene diamine was effective for the purpose of producing " 'regenerated cellulose consisting substantially entirely of skin' " whereas the prior art warned "this compound has 'practically no effect.' ").*

Although "[t]*he submission of evidence that a new product possesses unexpected properties does not necessarily require a conclusion that the claimed invention is nonobvious. In re Payne, 606 F.2d 303, 203 USPQ 245 (CCPA 1979). See the discussion of latent properties and additional advantages in MPEP § 2145,*" , the unexpected properties were unknown and non-inherent functions in view of Eisen or Lockhart'316, since they do not inherently achieve the same results. In other words, these advantages would not flow naturally from following their teachings, since Eisen or Lockhart'316 fail to suggest applying homology analysis among probes immobilized on a biochip thereby determining and displaying probe homologous similarity scores.

Applicants further contend that the mere fact that one of skill in the art could apply homology analysis to meet the terms of the claims is not by itself sufficient to support a finding of obviousness. The prior art must provide a motivation or reason for one skilled in the art to provide the unexpected properties, such as determining a probe homologous similarity score of two probes immobilized on a biochip thereby determining if unintended hybridization occurs, without the benefit of appellant's specification, to make the necessary

changes in the reference device. *Ex parte Chicago Rawhide Mfg. Co.*, 223 USPQ 351, 353 (Bd. Pat. App. & Inter. 1984). MPEP§2144.04 VI C.

None of the cited prior art references discloses, teaches or suggests the generating of a visually-intuitive graphical representation of the determined hybridization level and correspondingly determined probe homologous similarity scores of probes immobilized on a biochip to show unexpected or improper hybridization. The combination of these references would fall short of embodying a method having every feature of the present invention as claimed, most especially the features as noted above.

Further, since claims 2 - 9 recite features in addition to those in independent claim 1 that are already not shown by the cited prior art, these same references cannot be used to render obvious the more specific features of dependent claims 2 - 9. Rather, the present invention as a whole is distinguishable and thereby allowable over the prior art.

Conclusion

In view of all the above, Applicant respectfully submits that certain clear and distinct differences as discussed exist between the present invention as now claimed and the prior art references upon which the rejections in the Office Action rely. These differences are more than sufficient that the present invention as now claimed would not have been anticipated nor rendered obvious given the prior art. Rather, the present invention as a whole is distinguishable, and thereby allowable over the prior art.

Favorable reconsideration of this application as amended is respectfully solicited. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to

contact the Applicant's undersigned representative at the address and phone number indicated below.

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April 29, 2005

SPF/JCM/JT